Supporting Information

Double Stereodifferentiation in the “Acetate-Type” Aldol Reaction with Garner’s Aldehyde. Stereocontrolled Synthesis of Polyhydroxylated γ -Amino Carbonyl Compounds

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1.- Diastereoselective aldol reaction of pseudoephedrine acetamide (<i>R,R</i>)- 2a with chiral aldehyde 1	S2
2.- Hydrolysis of the adduct (<i>R,R</i>)- 3 . Synthesis of γ -amino- β,δ -dihydroxy acid 5 .	S3
3.- Esterification procedure. Synthesis of γ -amino- β,δ -dihydroxy ester 6	S3
4.- General procedure for the synthesis of γ -amino ketones 9a-f	S4

1.- Diastereoselective aldol reaction of pseudoephedrine acetamide (*R,R*)-2a with chiral aldehyde 1.

(-)-(1'*S*,1''*R*,2''*R*,4*R*)-4-{1'-Hydroxy-2'-[*N*-(2''-hydroxy-1''-methyl-2''-phenylethyl)-*N*-methylcarbamoyl]ethyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (*R,R*-3).

A solution of the acetamide (*R,R*)-2a (2.00 g, 9.66 mmol) in dry THF (15 mL) was slowly added to a cooled (-78°C) solution of LDA (20.29 mmol) in dry THF (50 mL). The mixture was stirred at this temperature for 1 h and allowed to reach to room temperature. After stirring for 30 min., the mixture was cooled down again to -105°C at which temperature a solution of chiral aldehyde **1** (3.32 g, 14.49 mmol) in dry THF (15 mL) was dropwise added within 20 min. The mixture was stirred at -105°C for 7 h and quenched with a saturated NH₄Cl solution (100 mL). The mixture was extracted with CH₂Cl₂ and the combined organic fractions were collected, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo* to yield a yellowish oil which was flash column chromatographed (hexanes/ethyl acetate 2:8) affording amide (*R,R*)-3 as a white solid (3.33 g, 7.63 mmol). Yield: 79%. Mp. 167-169°C (Et₂O). de = 96% (Chiracel OD column, UV detector, hexanes/*iso*-propanol 97: 3, Flow rate 0.85 mL/min, R_T for the (1'*S*,1''*R*,2''*R*,4*R*) isomer: 52.33 min. R_T for the (1'*R*,1''*R*,2''*R*,4*R*) isomer: 71.61 min.) [α]_D²⁰: -32.1 (1.0, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.81 (d, 3H, *J*= 7.1 Hz); 0.98* (d, 3H, *J*=6.7 Hz); 1.45 (bs, 15H); 2.55 (m, 2H); 2.85 (s, 3H); 2.88* (s, 3H); 3.65 (m, 1H); 3.86 (m, 1H); 4.23 (m, 1H); 4.49 (m, 2H); 4.89 (m, 1H); 5.53 (bs, 1H); 7.23-7.40 (m, 5H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 14.3; 15.2*; 23.8; 27.7; 28.1; 28.9*; 34.2; 54.3; 59.6; 60.6*; 64.6*; 64.9; 69.2*; 69.5; 75.1; 75.6*; 80.1*; 80.7; 93.7; 93.9*; 126.6*; 127.1; 127.6; 127.9*; 128.1; 128.3; 140.8; 141.4*; 152.2*; 153.2; 173.6*. IR (KBr): 3448 (OH); 1688; 1617 (C=O). MS (EI) *m/z* (Rel. Int.): 437 (M⁺+1, 5), 273 (25), 236 (36), 218 (50), 114 (34); 58 (100). Anal. Calcd. for C₂₃H₃₆N₂O₆: C, 63.28; H, 8.31; N, 6.42. Found. C, 63.37; H, 8.11; N, 6.50.

2.- Hydrolysis of the adduct (*R,R*)-3. Synthesis of γ -amino- β,δ -dihydroxy acid 5.

(+)-(1'*S*,4*R*)-4-(2'-Carboxy-1'-hydroxyethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (5).

A solution of the amide (*R,R*)-3 (0.56 g, 1.28 mmol) in THF (10 mL) was slowly added to a cooled (0°C) mixture of 4M NaOH (5 mL) and MeOH (5 mL). The mixture was then refluxed for 4h and allowed to reach to room temperature. More water (30 mL) was added and the mixture was washed with Et₂O (3x15 mL). After drying (Na₂SO₄), filtering and removing the solvents, the chiral auxiliary (*R,R*)-(-)-pseudoephedrine was recovered in 87% yield as a white solid after crystallization in hexane/AcOEt. The basic aqueous layer was then carefully basified with 1M HCl until pH=3 and the mixture was extracted with CH₂Cl₂ (3x15 mL). The combined organic fractions were collected, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo* to yield acid 5 (356 mg, 1.25 mmmol) as a yellowish oil without any further purification. Yield: 98%. $[\alpha]_D^{20}$: +13.4 (0.9, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ , ppm) 1.42 (s, 9H); 1.50 (s, 6H); 2.49 (m, 2H); 3.92-4.31 (m, 4H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ , ppm): 23.8; 26.6; 28.2; 37.8; 60.9; 64.8; 69.6; 81.5; 94.3; 153.9; 176.0. IR (CHCl₃): 3457 (OH); 1697; 1625 (C=O). MS (EI) *m/z* (Rel. Int.): 274 (M⁺-15, 1), 234 (4), 174 (9), 100 (25); 83 (7); 71 (7); 57 (100).

3.- Esterification procedure. Synthesis of γ -amino- β,δ -dihydroxy ester 6.

(+)-(1'*S*,4*R*)-4-(1'-Hydroxy-2'-methoxycarbonylethyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (6).

TMSCHN₂ (1.30 mL of a 2M solution in Et₂O, 2.61 mmol) was added over a cooled (0°C) solution of the acid 5 (189 mg, 0.65 mmol) in dry THF (10 mL). After stirring for 2h, MeOH (1 mL) was added at once and the mixture was stirred for further 45 min, after which it was quenched with water (15 mL). The mixture was extracted with CH₂Cl₂ (3x15 mL) and the combined organic fractions were collected, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo* to yield ester 6 (175 mg, 0.58 mmmol) as a colourless oil after flash column chromatography purification

(hexanes/AcOEt 1:1). Yield: 89%. $[\alpha]_D^{20}$: +15.28 (0.4, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ, ppm) 1.49 (s, 12H); 1.56 (s, 3H); 1.73 (m, 2H); 3.71 (s, 3H); 3.71-4.37 (m, 4H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ, ppm): 23.98; 26.7; 28.2; 37.9; 51.6; 61.18; 64.8; 69.9; 81.0; 94.2; 154.0; 172.7. IR (CHCl₃): 3455 (OH); 1739; 1697 (C=O). MS (EI) *m/z* (Rel. Int.): 288 (M⁺-15, 1), 200 (11), 188 (11), 144 (15); 100 (52); 83 (10); 57 (100). Anal. Calcd. for C₁₄H₂₅NO₆: C, 55.43; H, 8.31; N, 4.42. Found. C, 55.21; H, 8.13; N, 4.63.

4.- General procedure for the synthesis of γ-amino ketones 9a-f.

A solution of the corresponding organolithium reagent (3.5 eq.) was added over a cooled (-78°C) solution of the starting amide (1 eq.) in dry THF. After the addition was complete, the mixture was allowed to warm to 0°C and stirred for further 20 minutes. The reaction was quenched with 1M HCl (15 mL) and the mixture was extracted with CH₂Cl₂. After drying (Na₂SO₄), filtering and removing the solvent from the collected organic fractions the ketones **9a-f** were isolated after purification by flash column chromatography (hexanes/EtOAc 1:1). The chiral auxiliary (*R,R*)-(-)-pseudoephedrine was recovered in ca. 75% yield after basification of the aqueous layer and extraction (CH₂Cl₂, 3x15 mL) followed by drying (Na₂SO₄), filtering, and removing the solvent.

(+)-(1'S,4*R*)-4-(1'-Hydroxy-3'-oxobutyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (**9a**)

According to the general procedure, amide (***R,R*-3**) (260 mg, 0.77 mmol) was treated with MeLi (1.0 M solution in Et₂O, 2.70 mL, 2.70 mmol), affording ketone **9a** as a yellowish oil (207 mg, 0.72 mmol). Yield: 94%. $[\alpha]_D^{20}$: +15.2 (0.6, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ, ppm): 1.43 (s, 9H); 1.49 (s, 3H); 1.53 (s, 3H); 2.14 (s, 3H); 2.57 (m, 2H); 3.83-4.12 (m, 4H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ, ppm): 23.9; 27.0; 28.2; 30.7; 45.9; 60.7; 64.7; 65.1; 69.2; 94.1; 153.2; 205.6. IR (CHCl₃): 3445 (OH); 1705, 1655 (C=O). MS (EI) *m/z* (Rel. Int.): 246 (M⁺-41, 1), 200 (3); 170 (7); 144 (17); 100 (45); 87 (11); 85 (52); 83 (80), 57 (100). Anal. Calcd. for C₁₄H₂₅NO₅: C, 58.52; H, 8.77; N, 4.87. Found. C, 58.55; H, 8.86; N, 4.91.

(+)-(1'S,4R)-4-(1'-Hydroxy-3'-oxopentyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (9b)

According to the general procedure, amide (**R,R-3**) (155 mg, 0.46 mmol) was treated with EtLi (0.45 M solution in benzene/cyclohexane, 3.60 mL, 1.61 mmol), affording ketone **9b** as a yellowish oil (122 mg, 0.40 mmol). Yield: 88%. $[\alpha]_D^{20}$: +12.7 (0.3, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ, ppm): 0.97 (t, 3H, *J*=7.1Hz); 1.41 (s, 9H); 1.46 (s, 3H); 1.49 (s, 3H); 2.41 (m, 2H); 2.51 (m, 2H); 3.70-4.16 (m, 4H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ, ppm): 7.3; 23.9; 27.0; 28.1; 36.6; 36.9; 44.8; 60.7; 64.7; 69.2; 70.7; 93.9; 154.7; 211.9. IR (CHCl₃): 3450 (OH); 1708, 1660 (C=O). MS (EI) *m/z* (Rel. Int.): 258 (M⁺-43, 1), 200 (9); 176 (4); 144 (9); 100 (31); 85 (12); 83 (26), 57 (100). Anal. Calcd. for C₁₅H₂₇NO₅: C, 59.78; H, 9.03; N, 4.65. Found. C, 59.83; H, 8.96; N, 4.67.

(+)-(1'S,4R)-4-(1'-Hydroxy-4'-methyl-3'-oxopentyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (9c)

According to the general procedure, amide (**R,R-3**) (123 mg, 0.36 mmol) was treated with *i*-PrLi (0.62 M solution in pentane, 2.00 mL, 1.26 mmol), affording ketone **9c** as a yellowish oil (99 mg, 0.31 mmol). Yield: 87%. $[\alpha]_D^{20}$: +16.3 (0.6, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ, ppm): 1.09 (d, 6H, *J*=6.7Hz); 1.48 (s, 12H); 1.53 (s, 3H); 2.41 (m, 1H); 2.63 (m, 2H); 3.94-4.34 (m, 4H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ, ppm): 17.9; 24.1; 27.2; 28.3; 41.5; 42.9; 60.8; 63.2; 69.2; 80.8; 94.0; 152.5; 215.5. IR (CHCl₃): 3448 (OH); 1699, 1654 (C=O). MS (EI) *m/z* (Rel. Int.): 297 (M⁺-18, 1), 200 (10); 176 (40); 148 (16); 144 (15); 123 (10); 100 (52); 83 (15), 71 (15); 57 (100). Anal. Calcd. for C₁₆H₂₉NO₅: C, 60.93; H, 9.27; N, 4.44. Found. C, 61.10; H, 9.41; N, 4.38.

(+)-(1'S,4R)-4-(1'-Hydroxy-3'-oxoheptyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (9d)

According to the general procedure, amide (**R,R-3**) (112 mg, 0.26 mmol) was treated with *n*-BuLi (1.4 M solution in hexane, 0.64 mL, 0.90 mmol), affording ketone **9d** as a

yellowish oil (76 mg, 0.23 mmol). Yield: 89%. $[\alpha]_D^{20}$: +18.7 (0.7, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ , ppm): 0.87 (t, 3H, $J=7.9$ Hz); 1.27 (m, 4H); 1.46 (s, 15H); 2.42 (m, 2H); 2.56 (m, 2H); 3.93-4.17 (m, 4H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ , ppm): 13.7; 22.2; 24.0; 25.5; 27.1; 28.3; 43.2; 45.1; 60.8; 64.8; 69.3; 80.8; 94.1; 153.2; 211.9. IR (CHCl₃): 3482 (OH); 1699, 1670 (C=O). MS (EI) m/z (Rel. Int.): 274 (M^+ -55, 1), 200 (4); 176 (11); 144 (9); 100 (5); 85 (14), 83 (10); 57 (100). Anal. Calcd. for C₁₇H₃₁NO₅: C, 61.98; H, 9.48; N, 4.25. Found. C, 62.09; H, 9.55; N, 4.16.

(+)-(1'S,4R)-4-(1'-Hydroxy-4',4'-dimethyl-3'-oxopentyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (9e)

According to the general procedure, amide (**R,R-3**) (115 mg, 0.26 mmol) was treated with *t*-BuLi (1.0 M solution in hexane, 0.92 mL, 0.92 mmol), affording ketone **9e** as a yellowish oil (60 mg, 0.18 mmol). Yield: 71%. $[\alpha]_D^{20}$: +20.2 (0.4, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ , ppm): 1.13 (s, 9H); 1.49 (s, 15H); 2.67 (m, 2H); 3.68-4.19 (m, 4H). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ , ppm): 26.2; 27.3; 28.3; 29.1; 39.8; 44.4; 60.8; 64.9; 69.0; 80.7; 94.5; 153.2; 217.1. IR (CHCl₃): 3482 (OH); 1700, 1654 (C=O). MS (EI) m/z (Rel. Int.): 274 (M^+ -55, 1), 198 (5); 176 (15); 148 (10); 144 (9); 114 (3); 100 (32); 83 (12); 71 (7); 57 (100). Anal. Calcd. for C₁₇H₃₁NO₅: C, 61.98; H, 9.48; N, 4.25. Found. C, 61.83; H, 9.56; N, 4.22.

(+)-(1'S,4R)-4-(1'-Hydroxy-3'-oxo-3'-phenylpropyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (9f)

According to the general procedure, amide (**R,R-3**) (128 mg, 0.29 mmol) was treated with *t*-BuLi (2.0 M solution in Et₂O, 0.51 mL, 1.03 mmol), affording ketone **9f** as a yellowish oil (69 mg, 0.20 mmol). Yield: 68%. $[\alpha]_D^{20}$: +9.2 (0.12, CHCl₃). ¹H-NMR (250MHz, CDCl₃, 25°C, δ , ppm): 1.48 (s, 9H); 1.51 (s, 3H); 1.56 (s, 3H); 3.17 (m, 2H); 4.12-4.55 (m, 4H); 7.45-7.57 (m, 3H); 7.95 (d, 2H, $J=5.1$ Hz). ¹³C-NMR (250MHz, CDCl₃, 25°C, δ , ppm): 27.3; 28.3; 41.7; 60.9; 65.0; 69.4; 80.6; 94.3; 128.1; 128.6; 133.3; 141.6; 153.6; 198.6. IR (CHCl₃): 3447 (OH); 1695, 1645 (C=O). MS (EI) m/z (Rel. Int.): 275 (M^+ -74, 3), 216 (16); 176 (100); 148 (44); 117 (7); 105 (18); 100 (4); 91 (13); 77 (11); 57 (42). Anal. Calcd. for C₁₉H₂₇NO₅: C, 65.31; H, 7.79; N, 4.01. Found.

C, 65.39; H, 7.69; N, 3.91.